REMARKS

Rejection of Claims and Traversal Thereof

In the May 20, 2009 Office Action:

Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hancock (US Pub. No. 2002/0018776) in view of Baba, et al (Proc. Natl. Acad. Sci. USA, May 1999, vol. 96 pp. 5698-5703, hereinafter Baba; and

Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Vezina (WO94/05300) in view of Baba.

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

Rejection under 35 U.S.C. §103(a)

1. Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hancock in view of Baba and according to the Office, the combination of Hancock and Baba defeats the patentability of the presently claimed invention. Applicants insist that such a combination does not establish a *prima facie* case of obviousness.

Hancock describes a composition that includes an antagonist of CXC3 and an immune suppressant, wherein the composition is used to reduce graft rejections. Baba describes the use of TAK 779 as a CCR5 antagonist. Thus, the Office proposes that the teachings of these two references render the presently claimed invention as obvious. Applicants vigorously disagree.

Initially it should be noted that the combination of a CCR5 antagonist and the G1 phase arresting agent of the present invention provides for an entirely different outcome from that described in Hancock. Hancock is very concerned about an increase or continuous release of chemokines because they recruit more soldiers to the site of inflammation. Hancock wants to prevent the increase of chemokines because as shown in Table 4, an increase of chemokines is related to rejection of grafted tissue, recreated below for ease of reference:

TABLE 4

	SDF-1	Eotaxin	Lt	IP-10	Ran	Mig	MCP-1
no rejection	61%	45%	54%	29%	30%	6%	6%
rejection	64%	55%	36%	64%	55%	9%	0%

Hancock explicitly stated that RANTES and respective receptors can be associated with acute rejection. To prevent this increase of chemokines the Hancock group included an immunosuppressant to reduce the immune response. The list of immunosuppressive agents is set forth in paragraph 64 and includes a multiplicity of different choices, as shown below:

[0064] The term "immunosuppressive agent", as used herein, refers to compounds which can inhibit an immune response. The immunosuppressive agent used in the invention can be a novel compound or can be selected from the compounds which are known in the art, for example, calcineurin inhibitors (e.g., cyclosporin A, FK-506), IL-2 signal transduction inhibitors (e.g., rapamycin), glucocorticoids (e.g., prednisone, dexamethasone, methylprednisolone, prednisolone), nucleic acid synthesis inhibitors (e.g., azathioprine, mercaptopurine, mycophenolic acid) and antibodies to lymphocytes or antigen-binding fragments thereof (e.g., OKT3, anti-IL2 receptor). Novel immunosuppressive agents can be identified by those of skill in the art using suitable methods, for example, screening compounds for the capacity to inhibit antigen-dependent T cell activation.

[0065] The immunosuppressive agent used for co-therapy (e.g., co-administration with an antagonist of CXCR3 function) is preferably a calcineurin inhibitor. More preferably the immunosuppressive agent used for co-therapy is cyclosporin A.

Specifically, the Hancock group administers the immunosuppressive agent to lower the level of chemokines and prefers the use of cyclosporin A to induce this result.

Clearly even if we add Baba, the combination does not teach or suggest applicants' claimed invention. Applicants are concerned about reducing the level of the CCR5 receptor and causing the increase of chemokines because in fact when one has HIV the ability of an active immune system is essential. One

reading the Hancock reference would never consider using any information there in to go in the direction of applicants' claimed invention.

Applicants have surprisingly found that the addition of RAPA increases the level of chemokines as shown in Figure 3A, recreated below:

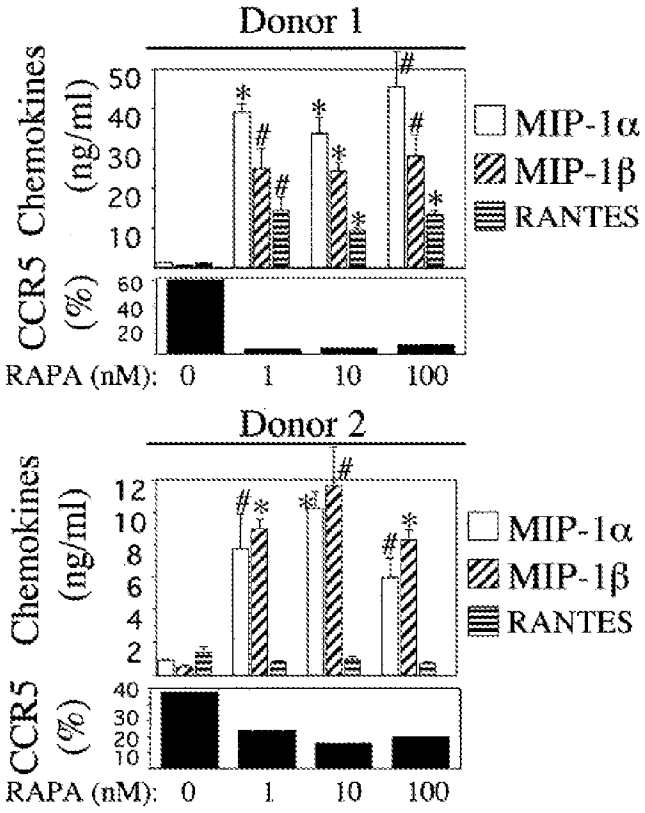
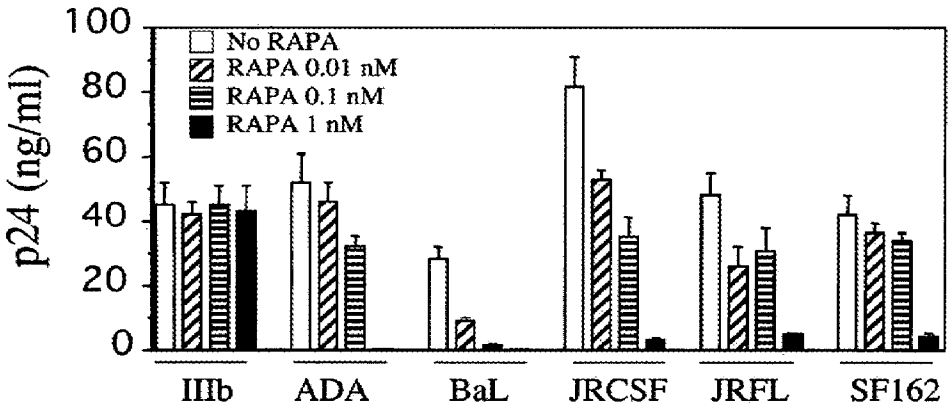


Figure 3A

More important by the use of rapamyacin, the level of HIV replication was reduced as shown in Figure 4C recreated below:



The different virus strain reacted with some variance but it is very evident that there was a reduction in the replication by using the RAPA.

The Office proposes that it would have been obvious to combine the compositions of Hancock and TAK 779 because TAK 779 is a small molecule that antagonizes CCR5. More important, according to the Office:

> "In regards to the effective amount of the G1 phase arresting compound sufficient enough to increase concentration of extrcellular beta-chemokine, Hancock teaches this limitation because the effective amount of the drugs is the sufficient to achieve a desired therapeutic effect."

This statement is surprising especially because Hancock uses an immunosuppressive agent to decrease the number of chemokines.

Under Graham, and as required by MPEP §§ 2111 and 2141.02, the Office must ascertain the differences between the claimed invention and the prior art, and must consider both the invention and **the prior art as a whole**. Thus, even in light of the *KSR* decision, **the Office must consider the inventions of any cited references in their respective entireties.** Certain individual features from the references may not be arbitrarily chosen (while equally arbitrarily discarding other disclosed features) to merely lump together disparate features of different references as a mosaic in an attempt to meet the features of the rejected claims. Thus, the Office is not allowed to pick and choose just certain parts of different references and combine them, **but instead, the references in their entirety must be considered. Thus the Office must recognize that Hancock teaches the reduction of chemokines NOT AN INCREASE.**

Considering the outcome from Hancock, applicants suggest that the cited reference teaches away from applicants' claimed invention. The Court in *In re Gurley*, 31 USPQ2d 1131 (Fed. Cir. 1994) addressed this very issue and stated:

> "[I]n general, a reference will teach away if it suggest that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. See United States v. Adams, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966) ("known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account for determining obviousness.)"

Further, the Court in *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 43 USPQ2d 1294 (Fed. Cir. 1997) provided further insight:

> " It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements....evidence that the combination was not viewed as technically feasible must be considered, for conventional wisdom that a combination should not be made is evidence of unobviousness."

Surely, anyone skilled in the art reading the Hancock reference alone or in combination with Baba would be discouraged from going in the direction that applicants have gone.

Further, the Hancock reference provides a laundry list of immunosuppressive agents but no guidance as to success of any of the compounds for the purpose of increasing beta-chemokines. The Office's contention that it would be obvious to make a composition comprising a G1 phase arresting agent and an antiviral agent that increases levels of beta-chemokines is similar to an "obvious to try" rejection. If this is the situation, it is important for the Office to review the "*In re Kubin*" ruling decided on April 3, 2009 because it provides guidance showing that the presently claimed invention is not obvious. (See I*n re Kubin*,90 USPQ2d 1417 (Fed. Cir. 2009))

Specifically, the *Kubin* Court revisited the *In re O'Farrell* decision (*In re O'Farrell*, 853 F.2d 894(Fed Cir. 1988)) and discussed that to differentiate between proper and improper applications of "obvious to try," the O'*Farrell* Court outlined two classes of situations where "obvious to try" is erroneously equated with obviousness under §103. In the first class of cases:

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

In such circumstances, wherein metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness.

The second class of *O'Farrell's* impermissible "obvious to try" situations occurs where

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Clearly the first class applies to the present invention. The cited prior art provides a laundry list of immunosuppressive agents but there is no guidance to go in the direction of applicants' claimed invention. Surely Hancock would never consider a treatment that increased the level of chemokines in combination with the described antagonists.

Importantly applicants have provided proof of the effectiveness of the presently claimed combination that not only shows increased levels of chemokines but reduced levels of HIV virus. The proposed combination does not teach or suggest these benefits.

As the Court stated in *Interconnect Planning Corp. v. Feil,* 227 USPQ 543 (Fed. Cir. 1985) "The invention must be viewed not with the blueprint drawn by the inventor, but **in the state of the art that existed at the time.**" (emphasis added) The state of the art existing at the time of the invention was characterized by understanding that combining an antagonist and immunosuppressive agent caused a reduction of chemokines. Nothing in the combination hinted of an increase in chemokines. Moreover, there is no suggestion or teaching that this combination would effectively increase an immune response and reduce replication of HIV.

In light of the above discussion, applicants request reconsideration and the withdrawal of this rejection for obviousness

2. Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Vezina in view of Baba. Applicants insist that such a combination does not establish a *prima facie* case of obviousness.

According to the Office, Vezina, et al (WO 94/05300) teaches the use of RAPA and an antiviral HIV agent that in combination with Baba defeats the patentability of the presently claimed invention.

Vezina, et al. describes a method of administering RAPA and a reverse transcriptase inhibitor to outbred athymic nude (nu/nu) mice. It should be noted that all *in vivo* testing described in Vezina, et al. was conducted in immunocompromised or immunodeficient animals and one skilled in the art would question whether such testing provides any guidance or hope of success for treatment in a human subject.

Still further, there are no tests results showing a working combination of RAPA with an antiviral agent. Instead the use of a reverse transcriptase was only used as a control. Thus there is no evidence that a combination of RAPA and AZT or any antiviral agent, administered concurrently would even be effective as an HIV treatment.

According to the Office, the Baba reference teaches the use of TAK 779 and proposes that it would be obvious to a skilled artisan to combine Vezina with Baba. Applicants insist that this general statement by the Office relating to HIV and pharmaceuticals is totally without merit. On logical grounds, given the possibility of adverse drug-drug interaction, the added constraint of dealing with different solubilities, bioavailability, biocompatibility, etc. and other practical difficulties of cocktail formulation, the *prima facie* obviousness of such approach is not at all evident as the "general proposition" put forward by the Office. Further, it is imperative that the Office recognizes that there are no working examples in Vezina that shows a combination of RAPA with an antiviral agent so the proposed combination of drugs has not been shown to be effective in the treatment of HIV.

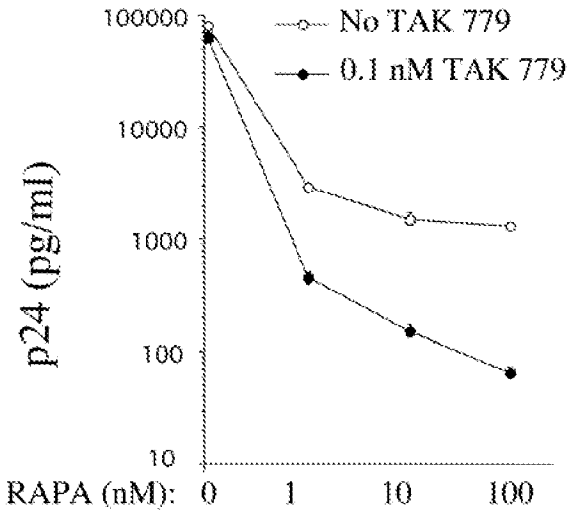
Applicants reiterate that the *Kubin* decision is relevant for the proposed combination. As stated above, the second class of *O'Farrell's* impermissible "obvious to try" situations occurs where

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Clearly this second class applies to the present invention. The cited prior art provides broad general statements but there is no guidance to go in the direction of applicants' claimed invention. Vezina has no working examples that include a combination of an anti viral agent in combination with RAPA, whether it is AZT or TAK 779. Thus, there may be general guidance but no indication as to what direction would be effective.

Clearly, applicants have shown improvement far surpassing any results shown in Vezina or Baba. Applicants have provided proof of the effectiveness of the presently claimed combination that includes a G1 phase arresting agent in combination with an agent that stops the HIV virus before entry into the cell.

As shown in Figure 6 of the application, and recreated below for ease of discussion,



and it is evident that there is impressive efficacy with the combination of RAPA and TAK 779. Clearly, 0.1 nM TAK-779 shows little antiviral activity and the results shown in Figure 4 (as set forth in the specification) indicate that administering RAPA alone reduces the level of P24 to nanograms/ml amounts. However, the combination of both agents reduces the levels of p24 to picograms/ml. Thus, the combination provides for a surprising reduction in replication of HIV-1.

Notably, by using the G1 phase arresting agent in combination with an antiviral that prevents the introduction of the virus into the cell, there is a double benefit of reducing landing sites for the virus and blocking any landing receptors that are available.

This impressive efficacy is also shown in Figure 7 when hydroxyurea is combined with TAK 779 as shown below:

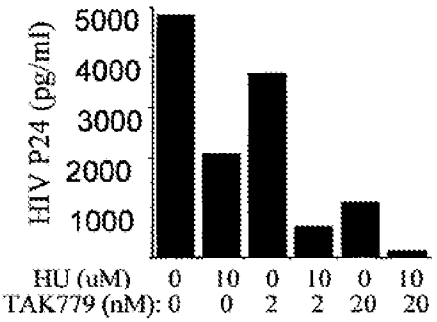


Figure 7

According to the Office, a skilled artisan would read the Baba reference and immediately disregard use of AZT of Vezina and instead use TAK 779 even if Vezina never shows the effectiveness of such combination. Applicants question where in either reference is there any suggestion that the proposed combination would be effective? There is none and the Office cannot speculation on such a combination, unless of course the Office is using applicants' specification as a blue print to go looking for ingredients. This type of hunting expedition would be using impermissible hindsight which is still considered unacceptable because the *KSR* Court expressly stated that a flexible TSM test remains the primary guarantor against **a non-statutory hindsight analysis such as the Office is using in the presently claimed invention.**

On July 21, 2008, the Federal Circuit expanded on post *KSR* establishment of a *prima facie* case of obviousness and stated in *Eisai Co. Ltd v Dr. Reddy Laboratories* 87 USPQ2d 1452 (Fed Cir 2008) that (1) *KSR* assumes a starting reference point, prior to the time of the invention, from which a skilled artisan might identify a problem and pursue potential solutions; (2) that the record up to the time of the invention would give some reason to make particular modifications; and (3) the record would provide some reason to narrow the prior art universe to a "finite number of identified and predictable solutions." Notably the *Eisai* Court further stated the "to the extent that an art is unpredictable, as in the chemical arts often are, *KSR's* focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

Applicants insist that after a review of the new guidelines for determination of obviousness and recent relevant case law, the Office cannot establish a *prima facie* case of obviousness and as such, applicants request that the rejection under 35 U.S.C. §103(a) be withdrawn.

Rejoinder of Method Claims

In accordance with Office guidelines recited in MPEP Section 821.04, when the elected product claims are found to recite patentable subject matter then the method claims that have been withdrawn may be rejoined and examined in this one application provided the method of use recite limitations corresponding to those found to be patentable during examination of the elected invention. As such, when the product claims are found to recite patentable subject matter, non-elected method claims 11, 12, 15-18, 23, 25, 27, 30, 33, 35, and 37-47 should be taken up for examination.

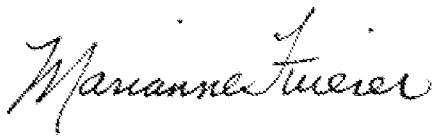
Fees Payable

No fee is due for entry of this response, however, if a fee is found due, the Commissioner is authorized to charge such fee to Deposit Account No. 13-4365 of Moore & Van Allen.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Carter reconsider the patentability of the pending claims in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. If any issues remain outstanding incident to the allowance of the application, Examiner Carter is requested to contact the undersigned attorney at (919) 286-8089.

Respectfully submitted,



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